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(54) Title: DISINFECTING CONTACT LENSES WITH BIS(BIGUANIDES) AND POLYMERIC BIGUANIDES

(57) Abstract

The present invention is directed to an ophthalmically safe disinfecting solution for contact lenses comprising a biguanide polymer in combination with a bis(biguanide), and a method of using the composition, in the form of an aqueous solution, for disinfecting and/or preserving contact lenses, especially soft contact lenses. The invention can be used to formulate products having greater convenience and/or benefits compared to traditional disinfecting products for contact lenses and can provide a broader, more potent and faster antimicrobial activity overall.

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DISINFECTING CONTACT LENSES WITH BIS(BIGUANIDES) AND POLYMERIC BIGUANIDES

Field of the Invention

This invention relates to new and improved solutions for the treatment of contact lenses and to methods for treating contact lenses with such solutions. In particular, the present invention is directed to disinfecting systems comprising the novel combination of two disinfecting agents, namely a bis(biguanide) and a polymeric biguanide.

Background of the Invention

Generally, contact lenses in wide use fall into three categories: (1) hard lenses formed from materials prepared by polymerization of acrylic esters, such as polymethyl methacrylate (PMMA), (2) rigid gas permeable (RGP) lenses formed from silicone acrylates and fluorosilicone methacrylates, and (3) gel, hydrogel or soft type lenses made of polymerized hydrophilic or hydrophobic monomers, such as 2-hydroxyethyl methacrylate (HEMA). The hard acrylic type contact lenses are characterized by low water vapor diffusion constants, resistance to the effects of light, oxygen and hydrolysis, and absorb only minor amounts of aqueous fluids. Because of the durability of hard contact lenses, coupled with their tendency not to absorb appreciable amounts of water, the selection of suitable disinfecting agents, cleaning agents or other lens care compounds is relatively non-critical.

However, unlike hard lenses, soft-type contact lenses have a tendency to bind and concentrate significantly more fluids, environmental pollutants, water impurities, as well as antimicrobial agents and other active ingredients commonly found in lens-care solutions. In most instances, the low levels of the ingredients in lens-care solutions do not lead to eye tissue irritation when used properly. Nevertheless, especially due to the inherent binding action of protein deposits to soft-lens materials, some disinfecting agents and preservatives tend to build up on lens surfaces and may become concentrated to potentially hazardous levels; such that when released could cause corneal inflammation and other eye tissue irritation.

Certain antibacterial agents were found to be more compatible with contact lenses and exhibit less binding on lens surfaces. In one case, it was found that chlorhexidine, a biguanide, binds to soft lens material seven times less than benzalkonium chloride. The presence of proteinaceous oily tear-film deposits on a lens, however, can double the amount of chlorhexidine absorbed on the lens compared to a clean lens. U.S. patent 4,354,952 discloses very dilute disinfecting and cleaning solutions containing chlorhexidine or its salt in combination with certain amphoteric and non-ionic surfactants. These solutions were found to reduce the amount of binding of chlorhexidine on hydrophilic soft contact lenses. Notwithstanding the reduction in binding achieved by this invention, the use of chlorhexidine did result in certain tradeoffs. The antimicrobial activity of the chlorhexidine may be diminished when used with certain amphoteric surfactants. Furthermore, it was reported that if not used in proper ratio, the surfactant and disinfectant will precipitate unless a non-ionic type surfactant is also employed.

British Patent 1,432,345 discloses contact lens disinfecting compositions containing a polymeric biguanide and a mixed phosphate buffer. Compositions as disclosed by this patent, however, have corneal staining values of 17% or more, far above that which is desirable for patient acceptability.

U.S. Patent 4,758,595 to Ogunbiyi et al. disclosed that a contact-lens solution containing a polyaminopropyl biguanide (PAPB), also known as polyhexamethylene biguanide (PHMB), has enhanced efficacy when combined with a borate buffer. These disinfecting and preservative solutions are especially noteworthy for their broad spectrum of bactericidal and fungicidal activity at low concentrations coupled with very low toxicity when used with soft-type contact lenses.

U.S. Patent No. 5,453,435 to Raheja et al., disclosed a preservative system that comprises a combination of chlorhexidine and polyhexamethylene biguanide. This preservative system, used in commercial products for rigid-gas-permeable lenses, was found to exhibit an improved combination of efficacy and low eye irritation.

Compositions containing PHMB and borate have been commercialized in various products, but at levels of about 1 ppm or less for use with soft contact lenses. It is generally desirable to provide the lowest level of a bactericide possible, while

maintaining the desirable level of disinfection efficacy, in order to provide a generous margin for safety and comfort.

Some of the most popular products for disinfecting lenses are multipurpose solutions that can be used to clean, disinfect and wet contact lenses, followed by direct insertion (placement on the eye) without rinsing. Obviously, the ability to use a single solution for contact-lens care is an advantage. Such a solution, however, must be particularly gentle to the eye, since, as indicated above, some of the solution will be on the lens when inserted and will come into contact with the eye.

With conventional contact-lens cleaners or disinfectants, including multi-purpose solutions, lens wearers typically need to digitally or manually rub the contact lenses (typically between a finger and palm or between fingers) during treatment of the contact lenses. The necessity for the daily "rubbing" of contact lenses adds to the time and effort involved in the daily care of contact lenses. Many contact-lens wearers dislike having to perform such a regimen or consider it to be an inconvenience. Some wearers may be negligent in the proper "rubbing" regimen, which may result in contact-lens discomfort and other problems. Sometimes rubbing, if performed too rigorously, which is particularly apt to occur with beginning lens wearers, may damage the lenses. This can be problematic when a replacement lens is not immediately available.

Contact lens solutions that qualify as a "Chemical Disinfecting Solution" do not require rubbing to meet biocidal performance criteria (for destroying representative bacteria and fungi) set by the US Food and Drug Administration (FDA) under the Premarket Notification (510k) Guidance Document For Contact Lens Care Products, May 1, 1997. In contrast, a contact-lens solution, referred to as a "Chemical Disinfecting System," that does not qualify as a Chemical Disinfecting Solution, requires a rubbing regimen to pass biocidal performance criteria. Traditionally, multi-purpose solutions (used for disinfecting and wetting or for disinfecting, cleaning, and wetting) have qualified as a Chemical Disinfecting System, but not as a Chemical Disinfecting Solution.

A Chemical Disinfecting Solution would generally require a more efficacious or stronger disinfectant than a Chemical Disinfecting System. The stronger the biocidal

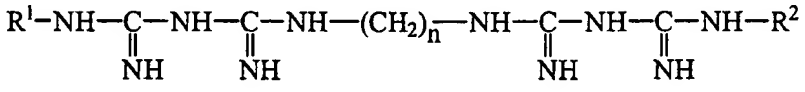
effect of a solution, however, the more likely that it may exhibit toxic effects or adversely effect lens-wearer comfort. For example, many very efficacious bactericides used in other contexts, such as mouthwashes, cosmetics, or shampoos, while being sufficiently safe for use in such products, would be too toxic for ophthalmic use, especially for use with soft lenses because of the above-mentioned tendency of soft lenses to bind chemicals and the sensitivity of eye tissues. Similarly, the concentrations of certain bactericides may need to be within lower limits in solutions for use with soft contact lenses than in other products or in solutions for other types of lenses, especially when such solutions are not rinsed from the contact lens before placing the lens in the eye.

It would be desirable to obtain a contact-lens solution that would simultaneously provide both (1) an increased level and/or broader spectrum of biocidal activity, and (2) a low order of toxicity to eye tissue, such that the solution can be used to treat a contact lens such that the lens can subsequently be placed on the eye without rinsing the solution from the lens. While challenging to develop, it would be especially desirable to obtain a Chemical Disinfecting Solution that could be used for soft contact lenses and that would allow direct placement of a contact lens on an eye following soaking in the solution and/or rinsing and rewetting with the solution. Such a product may provide increased efficacy, resulting in greater protection to the lens wearer against infection caused by microorganisms, while providing maximum convenience. Finally, it would be desirable for the biocidal efficacy of the disinfecting solution to be sufficiently high to achieve efficacious disinfection, or at least not inherently inefficacious disinfection, of a contact lens with respect to bacteria and fungi in the event, for whatever reason, that the contact lens wearer does not carry out a regimen involving mechanical rubbing or the like using the contact-lens solution.

Brief Description of the Invention

The present invention is directed to an ophthalmically safe disinfecting solution for contact lenses comprising:

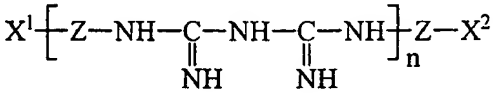
(a) about 0.10 to about 4.0 ppm of a bis(biguanide) in the form of a dihydrochloride salt, or a corresponding concentration of the same bis(biguanide) in the form of the free base or a different water-soluble salt, which bis(biguanide) has the following general formula:



(I)

or their water-soluble salt form, wherein R^1 and R^2 are independently selected from the group consisting of branched or unbranched alkyl, alkoxyalkyl or alkylsulfide radical, and n is 4 to 16; and

(b) about 0.1 to about 3.0 ppm of a polymeric biguanide having the formula:



(II)

wherein Z is an organic divalent bridging group which may be the same or different throughout the polymer, n on average is at least 3, and X^1 and X^2 are independently selected from the groups $-NH_2$ and -NH - C(=NH) - NH - CN.

(c) an effective amount of a buffering agent; and

(d) water in an amount of at least about 80% by weight.

Preferably, the compositions of the present invention also include one or more surfactants. In one embodiment of the invention, the surfactant is a neutral or non-ionic surfactant.

The invention is also directed to a method of disinfecting, or cleaning and disinfecting, a contact lens comprising soaking the lens for a given period of time in the aqueous solution described above, and subsequently directly placing the treated lens on

an eye of the wearer. In one embodiment of this method, a contact lens does not require rubbing with the solution to achieve the necessary disinfection.

Brief Description of the Drawings

FIG. 1 is a bar graph showing the biocidal efficacy, after 15 minutes, of a solution containing the combination of two disinfecting agents, namely a bis(biguanide) and a biguanide polymer, versus the theoretical sum of the biocidal efficacy of separate solutions of each disinfecting agent. The increased efficacy of the combination compared to the theoretical sum is a measure of the synergy of the combination. I n particular, Fig. 1 shows the theoretical log reduction compared to the actual log reduction for alexidine and PHMB, with respect to *C. albicans* microorganisms, after 15 minutes exposure.

FIG. 2 is a bar graph showing the biocidal efficacy, after 30 minutes, of a solution containing the combination of a bis(biguanide) and a biguanide polymer versus the theoretical sum of the biocidal efficacy of separate solutions of each disinfecting agent. In particular, Fig. 2. shows the theoretical log reduction compared to the actual log reduction for alexidine and PHMB, with respect to *C. albicans* microorganisms, after 30 minutes exposure.

Detailed Description of the Invention

As indicated above, the present invention is directed to a composition involving the combined used of a biguanide polymer and a bis(biguanide), and a method of using the composition, in the form of an aqueous solution, for disinfecting and/or preserving contact lenses, especially soft contact lenses. This synergistic combination offers maximum convenience while providing increased efficacy and hence better protection against microorganisms compared to traditional disinfecting products for contact lenses. The solution according to the present invention provides a broader, more potent and faster antimicrobial activity overall, when considering the entire range of microorganisms, based on representative bacteria and fungi commonly tested. In particular, the disinfecting solutions of the present invention are effective at low

concentrations against a wide spectrum of microorganisms, including but not limited to *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Serratia marcescens*, *Candida albicans*, and *Fusarium solani*.

A disinfecting solution is generally defined as a contact-lens care product containing one or more active ingredients (for example, anti-microbial agents and/or preservatives) in sufficient concentrations to destroy harmful microorganisms on the surface of a contact lens within the recommended minimum soaking time. The recommended minimum soaking time is included in the package instructions for use of the disinfecting solution. The term "disinfecting solution" does not exclude the possibility that the solution may also be useful as a preserving solution, or that the disinfecting solution may also be useful for other purposes such as daily cleaning, rinsing and storage of contact lenses, depending on the particular formulation. The present solution, in combination with its container or bottle and packaging, including instructions for use in accordance with a specified regimen, may be considered a novel and improved kit, package, or system for the care of contact lenses.

By the term "soft lens" is meant a lens having a proportion of hydrophilic repeat units such that the water content of the lens during use is at least 20% by weight. The term "soft contact lens" as used herein generally refers to those contact lenses which readily flex under small amounts of force. Typically, soft contact lenses are formulated from polymers having a certain proportion of repeat units derived from hydroxyethyl methacrylate and/or other hydrophilic monomers, typically crosslinked with a crosslinking agent. However, newer soft lenses, are being made from high-Dk silicone-containing materials.

By the term "ophthalmically safe" with respect to a contact-lens solution is meant that a contact lens treated with the solution is safe for direct placement on the eye without rinsing, that is, the solution is safe and comfortable for daily contact with the eye via a contact lens that has been wetted with the solution. An ophthalmically safe solution has a tonicity and pH that is compatible with the eye and comprises materials, and amounts thereof, that are non-cytotoxic according to ISO standards and U.S. FDA (Food & Drug Administration) regulations.

A solution that is useful for cleaning, chemical disinfection, storing, and rinsing a soft contact lens is referred to herein as a "multi-purpose solution." Multi-purpose solutions do not exclude the possibility that some wearers, for example, wearers particularly sensitive to chemical disinfectants or other chemical agents, may prefer to rinse or wet a contact lens with another solution, for example, a sterile saline solution prior to insertion of the lens. The term "multi-purpose solution" also does not exclude the possibility of periodic cleaners not used on a daily basis or supplemental cleaners for removing proteins, for example enzyme cleaners, which are typically used on a weekly basis. By the term "cleaning" is meant that the solution contains one or more cleaning agents in sufficient concentrations to loosen and remove loosely held lens deposits and other contaminants on the surface of a contact lens, especially if used in conjunction with digital manipulation (for example, manual rubbing of the lens with a solution) or with an accessory device that agitates the solution in contact with the lens, for example, a mechanical cleaning aid. The critical micelle concentration of a surfactant-containing solution is one way to evaluate its cleaning effectiveness.

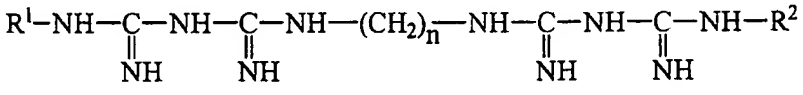
The term "effective multi-purpose solution" analogously refers to a solution useful for daily chemical disinfection, storing, and rinsing a contact lens, which solution does not claim to clean a contact lens, but which solution still obviates the need for any other solution for daily cleaning, that is, no other solution must necessarily be used in conjunction or combination with the solution on a daily basis. Although such solutions may comprise a surfactant or other agent that may inherently loosen or preventing lens deposits to some extent, such solutions are not necessarily capable of cleaning a contact lens. Effective multi-purpose solutions are therefore only applicable for lenses used for limited period of time, either disposable or frequent replacement lenses.

Traditionally, multi-purpose solutions on the market require a regimen involving mechanical rubbing of the contact lens with the multi-purpose solution, in order to provide the required disinfection. That is, such a regimen is required under governmental regulatory authorities (for example, the FDA or Food & Drug Administration in the USA) for a Chemical Disinfection System that does not qualify as a Chemical Disinfecting Solution. The invention according to the present invention has the advantage that it is possible to formulate a product that, on the one hand, is gentle

enough to be used as both a disinfecting solution and a wetting agent and, on the other hand, is able to meet the biocidal performance disinfection for a Chemical Disinfecting Solution under criteria established by the US FDA for Contact Lens Care Products (May 1, 1997) that does not require a regimen involving rubbing of the lenses (even though rubbing of the lens may provide further removal of microorganisms). In other words, the compositions according to the present invention may optionally be formulated to meet the requirements of the FDA or ISO Stand-Alone Procedure for contact lens disinfecting products. Accordingly, it is possible to make formulations that offer higher patient compliance and greater universal appeal than traditional disinfecting or disinfecting and cleaning products.

It is noted that the combination of the biguanide polymer and the bis(biguanide) provides enhanced efficacy while not causing irritation or discomfort to the eyes, always an important and challenging concern in the art of contact-lens care. Thus, increased amounts of the biguanide polymer, by itself, to achieve the same efficacy as the combination would result in greater eye irritation. Specifically, it has been found that increased amounts of the biguanide polymer, by itself, to achieve the necessary disinfection for a Chemical Disinfecting Solution would result in unacceptable eye irritation. Even if a rubbing regimen is recommended when using solutions of the present invention, the enhanced biocidal activity may provide greater protection against infection, especially if the rubbing by the contact-lens wearer is inadequate or omitted through negligence or disregard of the product instructions.

According to the present invention, the bis(biguanide) germicides employed in the present solutions include compounds, and their water-soluble salts, having following formula:



(I)

wherein R^1 and R^2 are independently selected (i.e., the same or different) from the group consisting of branched or unbranched alkyl having 4-12, preferably 6-10, carbon atoms, alkoxyalkyl (i.e., ether) or alkylsulfide (thioether or dialkylsulfide) radical having 4-12, preferably 6-10, carbon atoms, or cycloalkyl or cycloalkyl-alkyl radical having 5-12,

preferably 7-10, carbon atoms; and n is 4 to 16, preferably 6 to 10. By the term "cycloalkyl," either in cycloalkyl or cycloalkyl-alkyl, is meant unsubstituted or substituted cycloalkyl, where the substituents are one or more alkyl, alkoxy (-OR) , or alkylthio (-SR) groups having 1-6 carbon atoms.

In the present disinfecting solution, the biguanides of Formula (I) are suitably used in the total amount of 0.1 to 4.0 ppm, preferably 1.0 to 3.0 ppm based on the total aqueous solution. More preferably, the bis(biguanides) are used in the amount of 1.5 to 2.5, most preferably about 2.0 ppm. The concentration of the bis(biguanide) in solution is directly related to its bactericidal efficacy. The term "ppm" refers to "parts per million" and 1.0 ppm corresponds to 0.0001 percent by weight. It is based on the total weight of the composition or, in this case, the total weight of the aqueous disinfecting solution.

In the present application, the amount of the bis(biguanide) or other components in a solution according to the present invention refers to the amount formulated and introduced into the solution at the time the solution is made. Over time (for example, over a storage period of 18 months), the assayed amount of a bis(biguanide) in solution may decrease somewhat.

Preferably, the bis(biguanide) compounds have the above Formula (I) wherein R^1 and R^2 are independently selected from the group consisting of branched or unbranched alkyl, alkoxyalkyl (i.e., ether) or alkylsulfide (thioether) radical, and n is 5 to 7.

Each of R^1 and R^2 in Formulas (I) above may be, for example, an n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl, octyl, 2-ethylhexyl, dodecyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentylmethyl or cyclohexylmethyl radical. Preferred are 2-ethylhexyl (alexidine), 1,5-dimethylhexyl, 1-methylhexyl, 1,3-dimethylpentyl, 1,4-dimethylpentyl, cyclohexylmethyl, 2-norbornyl, propyloxyoctyl, and propyloxybutyl.

The acid-addition salts of the invention may be derived from an inorganic or organic acid. In most circumstances it is preferable that the salts be derived from an acid which is readily water soluble and which affords an anion which is suitable for human usage, for example a pharmaceutically-acceptable anion. Examples of such acids are hydrochloric, hydrobromic, phosphoric, sulphuric, acetic, D-gluconic, 2-pyrrolidino-5-

carboxylic, methanesulphonic, carbonic, lactic and glutamic acids. The hydrochloride salt is preferred.

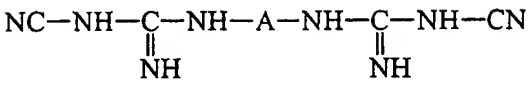
The bis(biguanides) of Formula (I) have relatively hydrophobic end groups. Preferably, the Log P of the compounds is 5 to 10, more preferably 6 to 8, wherein P is the partition coefficient of the free base, using the following equation, wherein C is the molar concentration of the bis(biguanide) in each phase and α is the degree of ionization of the bis(biguanide):

$$P = \frac{C_{octanol}}{C_{buffer}(1-\alpha)}$$

To obtain the partition coefficient of a bis(biguanide), the compound is partitioned between a 0.05 M phosphate buffer (pH 11) saturated with octanol and octanol saturated with phosphate buffer after gentle shaking at room temperature (26 °C). The volume ratio of these two phases and the amount of sample are chosen so that the absorbence of the sample from the buffered layer after partitioning has a value between 0.2 and 0.9, using a 1-cm cell and buffer solution as a blank. By working at a fixed pH and knowing or calculating the pK_a, the P value can be determined using the above formula. See "Quantitative Structure-Activity Relationships for Biguanides, Carbamidates, and Bisbiguanides as Inhibitors of Streptococcus mutans No. 6715", Warner, V. and Lynch, D., *J. Med. Chem*, 1979, Vol. 22, no. 4 at 359, 365; and Albert, and Serjeant, E., "Determination of Ionization and Stability Constants," Butler and Tanner Ltd., London, England, 1962, both references hereby incorporated by reference.

Particularly preferred bis(biguanide) compounds of this invention are 2-(decylthiomethyl)-pentane-1,5-bis(5-isopropylbiguanide), 2-(decylthio-methyl)pentane-1,5-bis(5,5-diethylbiguanide), and hexane-1,6-bis(2-ethylhexylbiguanide), the latter also known as alexidine or 1,1'-hexamethylenebis(5-(2-ethylhexyl)-biguanide) dihydrochloride. Other preferred bis(biguanides) include 1,1'-hexamethylenebis(5-heptyl-biguanide) dihydrochloride, 1,1'-hexamethylenebis(5-octyl-biguanide) dihydrochloride, and 1,1'-hexamethylenebis(5-hexyl-biguanide) dihydrochloride.

The biguanide compounds of Formula (I) may be made by reacting a bis-cyanoguanidine of the formula:

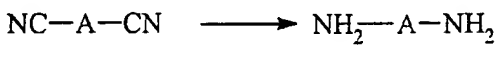


(VI)

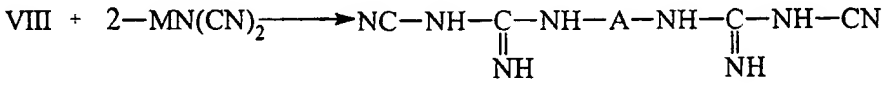
with an amine R^1NH_2, or with two different amines R^1NH_2 and R^2NH_2, in the form of an acid addition salt thereof, wherein R^1 and R^2 have the meanings stated above, at a temperature of 100°C to 170°C and A is an alkylene group having the required number of carbon atoms. A preferred amine salt is the hydrochloride. Most diamines are commercially available from a variety of sources.

The reactants are heated together until the reaction is complete. The reaction proceeds fastest at higher temperatures, but if thermal stability is a problem, the reaction should be carried out at lower temperature for a longer period. The reactants are most conveniently melted together in the absence of a solvent, but if desired an inert solvent such as DMSO, 2-methoxyethanol, 2-ethoxyethanol, nitrobenzene, sulpholane, isopropanol, n-butanol, ethylene glycol dimethyl ether or water, or a mixture of such solvents, may be used.

The bis-cyanoguanidine of the Formula (VI) may be manufactured from known starting materials such as hexamethylenedinitrile which is reduced, for example, with hydrogen and Raney nickel or with borane in dimethyl sulphide to the corresponding diamine (VIII), and the diamine in the form of an acid-addition salt, conveniently the dihydrochloride, is reacted with sodium dicyanamide or other suitable salt to form the required starting material (VI), as depicted below.

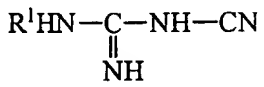


(VII) (VIII)



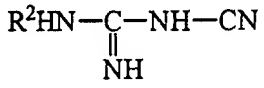
wherein M is a sodium, potassium, zinc or other suitable salt. The sodium salt is commercially available.

The compounds of the present invention can also be made by reacting a diamine of the Formula (VIII) in the form of an acid addition salt, with a cyanoguanidine of the formula:



(IX)

or with a cyanoguanidine of the Formula (IX) and a cyanoguanidine of the formula:



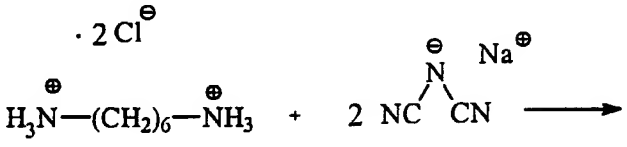
(X)

wherein R^1 and R^2 have the meanings stated above, at a temperature of 100° to 170°C.

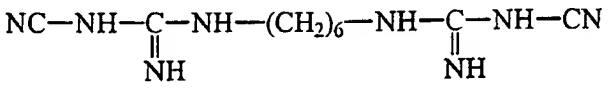
A suitable salt of the diamine is, for example, the dihydrochloride. The reactants are heated together until the reaction is complete. The reaction proceeds fastest at higher temperature, but if thermal stability is a problem, the reaction should be carried out at lower temperature over a longer period. If a melt can be formed at those temperatures the reactants are conveniently melted together in the absence of a solvent. If not, or alternatively, the reactants are heated together in a suitable inert solvent, for example those mentioned above. The acid-addition salts of the invention are obtained by conventional means.

The cyanoguanidines of the Formulae (IX) and (X), which may be used as starting materials in the above process, may be obtained by reacting sodium dicyanamide with an appropriate amine R^1NH_2 or R^2NH_2, in the form of an acid-addition salt, conveniently the dihydrochloride, in a suitable inert solvent.

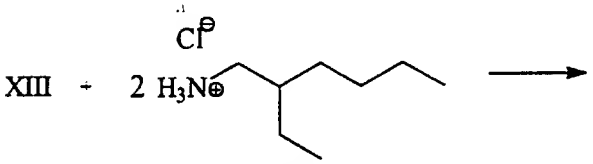
For example, the bis(biguanide) known as alexidine is produced from the following sequence of reactions.



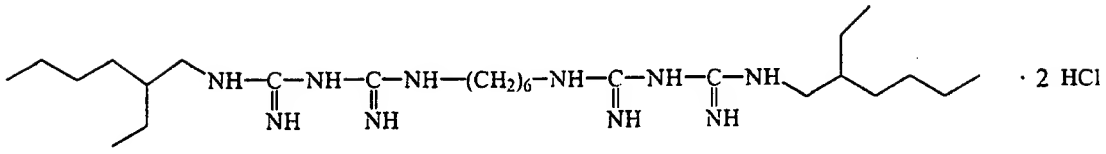
(XI) (XII)



(XIII)



(XIV)

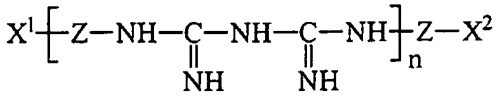


(XV)

Compound (XI) is hexamethylenediamine dihydrochloride (MW 189), Compound (XII) is sodium dicyanamide, Compound XIII is HMBDA, hexamethylene bis(cyanoguanido), Compound (XIV) is 2-ethyl-hexylamine hydrochloride (MW 165.7), and Compound (XV) is alexidine dihydrochloride a.k.a. [1,6-bis-(2-ethylhexylbiguanido]hexane dihydrochloride a.k.a. hexane-1,6-bis(2-ethylhexyl biguanide) dihydrochloride. This compound has a molecular weight in g/mole (MW) of 581.7 and empirical formula $C_{26}H_{56}N_{10}$-2HCl. The Compound (XV) is commercially available from various sources, including Sigma Chemical Co. (St. Louis, Missouri).

The methods for synthesized compounds of the present invention are also disclosed in European Patent Application Publication No. 0 125 092 (published 14.11.84); Rose, F.L. and Swain, G., "Bisdiguanide Having Antibacterial Activity," *J. Chem. Soc.*, p. 4422-4425 (1956); and Warner, Victor D. and Lynch, Donald, "Quantitative Structure-Activity Relationships of Biguanide, Carbamimidates, and Bisdiguanides as Inhibitors of Streptococcus Mutans No. 6715," *J. Med. Chem.*, Vol. 22, No. 6, p. 359-366 (1979).

The bis(biguanides) of the present invention (Formula I) may be used in combination with one or more polymeric biguanides, and water-soluble salts thereof, having the following formula:



(IV)

wherein Z is an organic divalent bridging group which may be the same or different throughout the polymer, n is on average at least 3, preferably on average 5 to 20, and X^1 and X^2 are independently selected from the groups $-NH_2$ and -NH - C(=NH) - NH - CN.

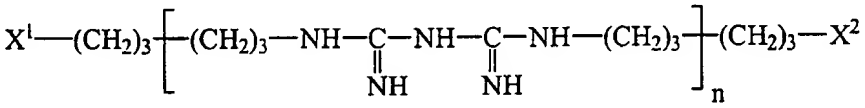
One preferred group of water-soluble polymeric biguanides will have number average molecular weights of at least 1,000 and more preferably will have number average molecular weights from 1,000 to 50,000. Suitable water-soluble salts of the free bases include, but are not limited to hydrochloride, borate, acetate, gluconate, sulfonate, tartrate and citrate salts.

The above-disclosed biguanides and methods of preparation are described in the literature. For example, U.S. patent 3,428,576 describes the preparation of polymeric biguanides from a diamine and salts thereof and a diamine salt of dicyanimide.

The polymeric biguanides, in combination with the bisbiguanides of the present invention, are effective in concentrations as low as 0.00001 weight percent (0.1 ppm). It has also been found that the bactericidal activity of the solutions may be enhanced or the spectrum of activity broadened through the use of a combination of such polymeric biguanides with the compounds of Formula (I) above. The effective amount of the

polymeric biguanides (irrespective of the particular salt form or whether the free base is used) may in total be as low as about 0.000010 weight percent (0.10 ppm) and up to about 0.00030 weight percent (3.0 ppm) in the present invention, whether in the form of a water-soluble salt or the free base. Preferably, the total amount of polymeric biguanide, in combination with the total amount of compounds of Formula (I) above is about 0.3 to 2.0 ppm, more preferably about 0.4 to 1.0, most preferably about 0.5 to 0.8 ppm.

Most preferred are the polymeric hexamethylene biguanides, commercially available, for example, as the hydrochloride salt from Zeneca (Wilmington, DE) under the trademark Cosmocil™ CQ. Such polymers and water-soluble salts are referred to as polyhexamethylene (PHMB) or polyaminopropyl biguanide (PAPB). The term PHMB or PAPB, as used herein, is meant to encompass one or more biguanides have the following formula:



(V)

wherein X^1 and X^2 are as defined above and n is from 1 to 500.

Depending on the manner in which the biguanides are prepared, the predominant compound falling within the above formula may have different X^1 and X^2 groups or the same groups, with lesser amounts of other compounds within the formula. Such compounds are known and are disclosed in US Patent No. 4,758,595 and British Patent 1,432,345, which patents are hereby incorporated herein by reference. Preferably, the water-soluble salts are compounds where n has an average value of 2 to 15, most preferably 3 to 12.

Optional additional disinfectant/germicide components may be employed in the present invention to further potentiate, compliment or broaden the spectrum of microbiocidal activity of the invention. This includes microbiocidally effective amounts of germicides which are compatible with and do not precipitate in the solution, in concentrations ranging from about 0.000001 to about 0.5 weight percent, depending on the particular disinfecting agent as will be appreciated by the skilled artisan. Suitable complementary germicidal agents include, but are not limited to thimerosol, sorbic acid,

alkyl triethanolamines, phenylmercuric salts, quaternary ammonium compounds, and polyquaternium copolymers, and mixtures thereof. Suitable salts are soluble in water at ambient temperature to the extent of at least 0.5 weight percent. These salts include the gluconate, isethionate, (2-hydroxyethanesulfonate), formate, acetate, glutamate, succinanate, monodiglycollate, methanesulfonate, lactate, isobutyrate and glucoheptonate. Representative examples of the quaternary ammonium compounds are compositions comprised of balanced mixtures of n-alkyl dimethyl benzyl ammonium chlorides. An example of a polyquaternium polymer used in ophthalmic applications include Polyquaternium 1® (chemical registry number 75345-27-6) available from Onyx corporation.

The present solution optionally comprises at least one surfactant. Suitable surfactants can be either amphoteric, cationic, anionic, or nonionic which may be present (individually or in combination) in amounts up to 15 percent, preferably up to 5 percent by weight of the composition or solution. Preferred surfactants are amphoteric or nonionic surfactants, which when used impart cleaning and conditioning properties. The surfactant should be soluble in the lens care solution and non-irritating to eye tissues. Many nonionic surfactants comprise one or more chains or polymeric components having oxyalkylene (-O-R-) repeats units wherein R has 2 to 6 carbon atoms. Preferred non-ionic surfactants comprise block polymers of two or more different kinds of oxyalkylene repeat units, which ratio of different repeat units determines the HLB of the surfactant. Satisfactory non-ionic surfactants include polyethylene glycol esters of fatty acids, e.g. coconut, polysorbate, polyoxyethylene or polyoxypropylene ethers of higher alkanes (C_{12}-C_{18}). Examples of the preferred class include polysorbate 20 (available under the trademark Tween® 20), polyoxyethylene (23) lauryl ether (Brij® 35), polyoxyethyene (40) stearate (Myrj® 52), polyoxyethylene (25) propylene glycol stearate (Atlas® G 2612). One non-ionic surfactant in particular consisting of a poly(oxypropylene)-poly(oxyethylene) adduct of ethylene diamine having a molecular weight from about 7,500 to about 27,000 wherein at least 40 weight percent of said adduct is poly(oxyethylene) has been found to be particularly advantageous for use in cleaning and conditioning both soft and hard contact lenses when used in amounts from

about 0.01 to about 15 weight percent. The CTFA Cosmetic Ingredient Dictionary's adopted name for this group of surfactants is poloxamine. Such surfactants are available from BASF Wyandotte Corp., Wyandotte, Michigan, under the registered trademark "Tetronic". An analogous of series of surfactants, suitable for use in the present invention, is the poloxamer series which is a poly(oxyethylene) poly(oxypropylene) block polymers available under the trademark "Pluronic" (commercially available form BASF).

Various other ionic as well as amphoteric and anionic surfactants suitable for in the invention can be readily ascertained, in view of the foregoing description, from McCutcheon's Detergents and Emulsifiers, North American Edition, McCutcheon Division, MC Publishing Co., Glen Rock, NJ 07452 and the CTFA International Cosmetic Ingredient Handbook, Published by The Cosmetic, Toiletry, and Fragrance Association, Washington, D.C.

Amphoteric surfactants suitable for use in a composition according to the present invention include materials of the type are offered commercially under the trade name "Miranol." Another useful class of amphoteric surfactants is exemplified by cocoamidopropyl betaine, commercially available from various sources.

The foregoing surfactants when employed with a buffer enhancer will generally be present in an amount from 0.01 to 5.0 percent (w/w), preferably 0.1 to 5.0 percent.

Typically, the aqueous solutions of the present invention for treating contact lenses are also adjusted with tonicity agents, to approximate the osmotic pressure of normal lacrimal fluids which is equivalent to a 0.9 percent solution of sodium chloride or 2.5 percent of glycerol solution. The solutions are made substantially isotonic with physiological saline used alone or in combination, otherwise if simply blended with sterile water and made hypotonic or made hypertonic the lenses will lose their desirable optical parameters. Correspondingly, excess saline may result in the formation of a hypertonic solution which will cause stinging and eye irritation.

The pH of the present solutions should be maintained within the range of 5.0 to 8.0, more preferably about 6.0 to 8.0, most preferably about 6.5 to 7.8, suitable buffers may be added, such as boric acid, sodium borate, potassium citrate, citric acid, sodium bicarbonate, TRIS, and various mixed phosphate buffers (including combinations of

Na_2HPO_4, NaH_2PO_4 and KH_2PO_4) and mixtures thereof. Borate buffers are preferred, particularly for enhancing the efficacy of biguanides. Generally, buffers will be used in amounts ranging from about 0.05 to 2.5 percent by weight, and preferably, from 0.1 to 1.5 percent. The disinfecting/preserving solutions of this invention preferably contain a borate buffer system, containing one or more of boric acid, sodium borate, potassium tetraborate, potassium metaborate, or mixtures of the same.

In addition to buffering agents, in some instances it may be desirable to include sequestering agents in the present solutions in order to bind metal ions which might otherwise react with the lens and/or protein deposits and collect on the lens. Ethylene-diaminetetraacetic acid (EDTA) and its salts (disodium) are preferred examples. They are usually added in amounts ranging from about 0.01 to about 0.2 weight percent. Other suitable sequestering agents include gluconic acid, citric acid, tartaric acid and their salts, e.g. sodium salts. Preferred sequestering agents, which are also effective for removing protein deposits, are the phosphonate compounds disclosed in WO 97/31659.

The aqueous solutions of the present invention are especially useful for soft contact lenses, with or without further additives. Nevertheless, the solutions of the present invention may be formulated into specific contact lens care products, such as wetting solutions, soaking solutions, cleaning and conditioning solutions, as well as multi-purpose type lens care solutions, etc. and mixtures thereof. Finally, such solutions can be applied to the lenses outside the eye or while on the eye, for example, in the form of droplets.

It may also be desirable to include water-soluble viscosity builders in the solutions of the present invention. Because of their demulcent effect, viscosity builders have a tendency to enhance the lens wearer's comfort by means of a film on the lens surface cushioning impact against the eye. Included among the water-soluble viscosity builders are the cellulose polymers like hydroxyethyl or hydroxypropyl cellulose, carboxymethyl cellulose, povidone, polyvinyl alcohol, and the like. Such viscosity builders may be employed in amounts ranging from about 0.01 to about 4.0 weight percent or less. The present solutions may also include optional demulcents.

The aqueous solutions according to the present invention can be effectively used in disinfecting contact lenses by any of the well recognized methods. The lenses may be treated by the "cold" soaking method at room temperature for a period ranging from about 5 minutes to about 12 hours. The lenses are then removed from the solution, rinsed with the same or a different solution, for example a preserved isotonic saline solution and then replaced on the eye.

As indicated above, contact-lens wearers are commonly required to digitally or manually rub the contact lenses (typically between a finger and palm or between fingers) during daily cleaning and/or disinfecting of contact lenses. In one embodiment of the present invention, a method is provided in which rubbing is not required during treatment with the claimed specified solution, between removal from the eye and replacement of the lens following lens care. In a preferred embodiment of such a method, a soft lens is disinfected or both disinfected and cleaned with a multipurpose solution or an effective multipurpose solution that is the only daily solution needed for treating the lens outside the eye. Thus, in one embodiment of a method according to the invention, the described solution is used to treat a contact lens without rubbing, by a method comprising:

(a) soaking the contact lens that has not been rubbed with the solution for a specified time period, and

(b) direct placement of the treated contact lens on the eye of the wearer.

Typically, step (a) may involve immersing the contact lens in the solution. Soaking may optionally comprise shaking or similarly agitating a container of the solution by manual means. Preferably, step (a) involves a period of soaking the contact lens in a container wherein the contact lens is completely immersed in the solution. By the term "direct placement" is herein meant that the solution is not diluted or rinsed off the lens with a different contact-lens solution prior to "insertion" or placement on the eye. In a particularly preferred embodiment, the method uses a product that is formulated as a multi-purpose or effective multi-purpose solution, wherein no other solution or product is required for daily cleaning of the lens, with the possible exception of an enzyme cleaner.

In yet another embodiment of a method according to the present invention, the claimed solution is used to clean a frequent replacement lens (FRL) that is planned for replacement after not more than about three months of use in the eye, or that is planned for replacement after not more than about 30 days of use in the eye, or that is planned for replacement after not more than about two weeks in the eye. Preferably, the lens is made from a polymer comprising about 0.0 to 5 mole percent repeat units derived from methacrylic acid (MAA), 10 to 99 mole percent of repeat units derived from hydroxyethyl methacrylate, and about 0.5 to 5 mole percent of cross-linking repeat units. Cross-linking repeat units may be derived, for example, from such monomers as ethyleneglycol dimethacrylate, divinylbenzene, and trimethylpropane trimethacrylate.

The following Examples illustrate the compositions and methods of the instant invention.

EXAMPLE 1

This Example illustrates the preparation of 1,6 bis(cyanoguanidino) hexane, used as a starting material for bis(biguanides) of the present invention. In the amount of 35.80 g (0.402 mole), sodium dicyanamide (NaC_2N_3) is suspended in 400 mL of 1-butanol. Then, 23.60 g (0.204 mole) of 1,6-hexanediamine were added as well as 33.0 mL of conc. aqueous hydrochloric acid (0.400 mole). A milky white precipitate appeared immediately which was probably the amine hydrochloride. The mixture was then refluxed for 3.5 hr. The suspension was then cooled to room temperature and filtered. The white solid was then washed well with distilled water before drying under vacuum. Yield 46.38 g; 93.1%. C 10 H 18 N 8 calc'd: C 48.0%; H 7.20%; N 44.80%; found: C 47.7%; H 7.40%; N 45.12%. 300 MHz ^{1}H NMR (d^6-DMSO) 6.60 ppm (6p, br m); 2.93 ppm (4p, m); 1.34 ppm (4p, br s); 1.15 ppm (4p, br s). IR (KBr pellet, cm^{-1}) 3142 (m); 2943; 2912; 2862 (w); 2179 (s); 1658; 1609 (s).

EXAMPLE 2

This Example illustrates the preparation of the bis(biguanide) known as alexidine for use in the present invention. Hexamethylene bis(cyanoguanido) in the amount of 1.003g (0.004498 moles) was placed into a flask. To this was added 1.474 mL (1.163g;

0.008996 moles) of 2-ethylhexylamine. Then, 0.74 mL (0.008996 moles) of concentrated HCl was added. The mixture was heated in a flask to boil away the H_2O. After the H_2O was gone, the temperature of the melt had risen to 195°C. The temperature was decreased to 150-160°C and maintained for 1 hour. The material was cooled to room temperature. The solid can be dissolved in hot water and allowed to crystallize.

EXAMPLE 3

This Example illustrates the preparation of poly(hexamethylene biguanide), also referred to as PAPB or PHMB, for use in combination with bis(biguanides) in the present invention. In 500 mL of distilled water was suspended 25.08 g (0.100 mole) of 1,6-bis(cyanoguanidino)hexane and 18.99 g (0.100 mole) of 1,6-hexanediamine dihydrochloride. The pH of this mixture was then brought down to 6.8 with dilute hydrochloric acid. The water was then removed by distillation under reduced pressure. The white solid was then transferred to a three-necked flask fitted with a mechanical stirrer and heating mantle. The intimate mixture of solids was then placed under nitrogen and the temperature of the mixture was raised to 150-55°C. The molten reaction mixture possessed the consistency of honey. The mixture was stirred at 150-55°C for 1 - 1.5 hr. before cooling to room temperature. The resulting poly(hexamethylene biguanide) is obtained as a glassy solid. The yield is essentially quantitative. Melting range 105-125°C. 300 MHz ^{1}H NMR (D_2O) 3.13 ppm (21.1p, br t); 2.93 ppm (2p, t); 1.49 ppm (21.1p, br s); 1.28 ppm (21.1p, br s). IR (KBr pellet, cm^{-1}) 3325; 3201 (s); 2931; 2858 (m); 2175 (m-w); 1631; 1589; 1550(s).

EXAMPLE 4

This example illustrates the preparation of an aqueous disinfecting solution according to the present invention comprising a combination of alexidine and polyhexamtheylene biguanide (also referred to as PHMB). The following components are used, in the indicated percent weight per total volume of the solution:

	Percent (w/v)
PHMB	0.00008
Alexidine•2HCl	0.0002
Poloxamine 1107**	1.0
Na_2EDTA	0.11
Boric Acid	0.66
Sodium Borate	0.10
Sodium Chloride	0.54
Distilled Water (qs)	100.0

** molecular weight 14,500, Tetronic® 1107, a poly(oxypropylene) poly(oxyethylene) block copolymer adduct of ethylene diamine, a trademark of BASF Wyandotte Corp., Wyandotte, MI.

The solution is prepared by gradually heating 80 percent of the water to 80°C while dissolving the disodium EDTA therein. The boric acid and sodium borate are added to the heated solution of disodium EDTA and dissolved. The sodium chloride is then added to the solution and dissolved, followed by the addition of the surfactant. The solution is sterilized by autoclaving to 120°C for 45 minute. After the solution is cooled to room temperature, the alexidine bis(biguanide) and the PHMB are added as a solution through a sterile filter, followed by the balance of distilled water. The solution is packaged in sterilized plastic containers.

EXAMPLE 5

This Example illustrates the improved antimicrobial efficacy of the combination of alexidine with polyhexamethylene biguanide (PHMB) in an aqueous disinfecting solution for contact lenses. The antimicrobial efficacy of each of various compositions for the chemical disinfection of contact lenses was evaluated.

Microbial challenge inoculums were prepared using *Pseudomonas aeruginosa* (ATCC 9027), *Staphylococcus aureus* (ATCC 6538), *Serratia marcescens* (ATCC 13880), *Candida albicans* (ATCC 10231), and *Fusarium solani* (ATCC 36031). The test organisms were cultured on appropriate agar and the cultures were harvested using sterile DPBST (Dulbecco's Phosphate Buffered Saline plus 0.05% w/v polysorbate 80) or a suitable diluent and transferred to a suitable vessel. Spore suspensions were filtered

through sterile glass wool to remove hyphal fragments. *Serratia marcescens*, as appropriate, was filtered (eg., through a 1.2μ filter) to clarify the suspension. After harvesting, the suspension was centrifuged at no more than 5000 x g for a maximum of 30 minutes at 20-25°C. The supernatant was poured off and resuspended in DPBST or other suitable diluent. The suspension was centrifuged a second time, and resuspended in DPBST or other suitable diluent. All challenge bacterial and fungal cell suspensions were adjusted with DPBST or other suitable diluent to 1 x 10^7-10^8 cfu/mL. The appropriate cell concentration may be estimated by measuring the turbidity of the suspension, for example using a spectrophotometer at a preselected wavelength, for example 490 nm. One tube was prepared containing a minimum of 10 mL of test solution per challenge organism. Each tube of the solution to be tested was inoculated with a suspension of the test organism sufficient to provide a final count of 1.0 x 10^5-10^6 cfu/mL, the volume of the inoculum not exceeding 1% of the sample volume. Dispersion of the inoculum was ensured by vortexing the sample for at least 15 seconds. The inoculated product was stored at 10-25°C. Aliquots in the amount of 1.0 mL were taken of the inoculated product for determination of viable counts after certain time periods of disinfection. The time points for the bacteria were, for example, 1, 2, 3, and 4 hours when the proposed regimen soaking time was 4 hours. Yeast and mold were tested at an additional time point of ≥ 16 hours (4 times the regimen time). The suspension was mixed well by vortexing vigorously for at least 5 second. The 1.0 mL aliquots removed at the specified time intervals were subjected to a suitable series of decimal dilutions in validated neutralizing media. The suspensions were mixed vigorously and incubated for a suitable period of time to allow for neutralization of the microbial agent. The viable count of organisms was determined in appropriate dilutions by preparation of triplicate plates of trypticase soy (TSA) agar for bacteria and Sabouraud dextrose agar (SDA) for mold and yeast. The bacterial recovery plates were incubated at 30-35°C for 2-4 days. The yeast was incubated at 20-30°C for 2-4 days and mold recovery plates at 20-25°C for 3-7 days. The average number of colony forming units was determined on countable plates. Countable plates refer to 30-300 cfu/plates for bacteria and yeast, and 8 to 80 cfu/plate for mold except when colonies are observed only for the 10^0 or 10^{-1} dilution plates. The microbial reduction was then calculated at the specified time points. In order

to demonstrate the suitability of the medium used for growth of the test organisms and to provide an estimation of the initial inoculum concentration, inoculum controls were made by dispersing an identical aliquot of the inoculum into a suitable diluent, for example DPBST, using the same volume of diluent used to suspend the organism as listed above. Following inoculation in a validated neutralizing broth and incubation for an appropriate period of time, the inoculum control must be between 1.0×10^5 - 1.0×10^6 cfu/mL

The solutions were evaluated based on the performance requirement referred to as the "Stand-Alone Procedure for Disinfecting Products" (hereafter the "stand-alone test") and is based on the Disinfection Efficacy Testing for contact lens care products under the Premarket Notification (510(k)) Guidance Document For Contact Lens Care Products dated May 1, 1997, prepared by the U.S. Food and Drug Administration, Division of Ophthalmic Devices. This performance requirement is comparable to current ISO standards for disinfection of contact lenses (revised 1995). The stand-alone test challenges a disinfecting product with a standard inoculum of a representative range of microorganisms and establishes the extent of viability loss at pre-determined time intervals comparable with those during which the product may be used. The primary criteria for a given disinfection period (corresponding to a potential minimum recommended disinfection period) is that the number of bacteria recovered per mL must be reduced by a mean value of not less than 3.0 logs within the given disinfection period. The number of mold and yeast recovered per mL must be reduced by a mean value of not less than 1.0 log within the minimum recommended disinfection time with no increase at four times the minimum recommended disinfection time.

The testing procedures described above were followed to determine whether the primary performance criteria would be passed at time intervals of 5 minutes, 15 minutes, 30 minutes, and 4 hours. The concentration of alexidine in this set of tests was formulated in amounts ranging from 0.0 to 4.0 ppm in combination with either 0.0 or 0.8 ppm PAPB, the latter the amount of PAPB currently used in commercial multi-purpose solutions for soft contact lenses. The results are shown in Table 1 below.

TABLE 1

Alexidine• 2HCl (ppm)	PAPB (ppm)	Soak Period	Log Reduction *S. marcescens*	Log Reduction *C. albicans*
0.5	0.8	5 min	-	0.6
		15 min	2.0	1.1
		30 min	3.2	1.8
		60 min	4.3	3.5
1.0	0.8	5 min	-	0.5
		15 min	2.6	1.1
		30 min	3.7	2.2
		60 min	>4.3	4.2
2.6	0.8	5 min	-	0.7
		15 min	2.7	2.2
		30 min	>4.3	3.3
		60 min	>4.3	>4.2
4.0	0.8	5 min	-	1.1
		15 min	>4.3	3.0
		30 min	>4.3	>4.2
		60 min	>4.3	>4.2
0.5	0.0	5 min	-	0.3
		15 min	0.6	1.0
		30 min	1.6	-0.2
		60 min	2.5	-0.1
2.6	0.0	5 min	-	0.4
		15 min	2.2	0.5
		30 min	>4.3	0.5
		60 min	>4.3	1.4
0.0	0.8	15 min	-	0.6
		30 min	1.3	0.8
		45 min	2.0	1.4
		60 min	3.1	2.9

The results show that the addition of alexidine to the polyhexametheylene biguanide improved antimicrobial efficacy, with the improved efficacy reaching a trade-off, for practical purposes, at about 4.0 ppm, such that any improved antimicrobial efficacy would be unlikely to be justified by the increased potential for toxicity at higher concentrations of the antimicrobial agent. With respect to *C. albicans*, there appears to be a synergistic effect at time periods of 15 minutes and 30 minutes, with the combination of 2.6 ppm alexidine and 0.8 ppm PAPB showing greater efficacy than the sum of 2.6 ppm alexidine by itself and 0.8 ppm PAPB by itself.

EXAMPLE 6

This Example illustrates the microbiocidal efficacy of solutions according to the present invention. The above testing procedures were used for evaluating the antimicrobial efficacy against C. *albicans* of disinfecting solutions such as prepared in Example 4, but which contain the bis(biguanide) alexidine at various concentrations extending from 1 ppm to 4 ppm and the biguanide polymer at various concentrations extending from 0.3 to 1.5 ppm. The results are shown in Table 2 after a 5 minute soak, Table 3 after a 15 minute soak, Table 4 after a 30 minute soak, and Table 5 after a 45 minute soak. Tables 6 to 9, corresponding respectively to Tables 2 to 5, compares the theoretical kill, based on the sum of individual disinfecting agents versus actual kill using the combination of disinfecting agents. For this calculation, the following equation was employed: log 10(exp10(PHMB) + exp10(alexidine)). In other words, to calculate the theoretical log kill, the log reduction kill values for each separate disinfecting agent were converted to the numbers of organisms killed, and then these values were added and a new log value derived for the sum.

TABLE 2
(5 Minutes)

		PHMB			
		0 ppm	**0.3 ppm**	**0.8 ppm**	**1.5 ppm**
Alexidine	0 ppm	0.4	0.4	0.7	1.0
	1 ppm	0.5	0.6	0.9	1.1
	2 ppm	0.7	0.8	0.9	1.5
	3 ppm	0.8	1.1	1.6	2.6
	4 ppm	1.1	1.8	2.8	3.4

TABLE 3
(15 Minutes)

		PHMB			
		0 ppm	0.3 ppm	0.8 ppm	1.5 ppm
Alexidine	0 ppm	0.4	0.7	1.5	1.9
	1 ppm	0.4	1.1	2.2	2.9
	2 ppm	0.8	1.7	2.8	3.5
	3 ppm	1.6	2.7	3.7	4.5
	4 ppm	2.6	3.8	4.8	>4.8

TABLE 4
(30 Minutes)

		PHMB			
		0 ppm	0.3 ppm	0.8 ppm	1.5 ppm
Alexidine	0 ppm	0.4	1.0	2.1	3.1
	1 ppm	0.5	1.8	3.3	4.4
	2 ppm	1.2	2.1	3.7	4.5
	3 ppm	1.9	3.5	4.8	>4.8
	4 ppm	3.4	>4.8	>4.8	>4.8

TABLE 5
(45 Minutes)

		PHMB			
		0 ppm	**0.3 ppm**	**0.8 ppm**	**1.5 ppm**
Alexidine	0 ppm	0.4	1.1	3.0	4.1
	1 ppm	0.4	2.1	3.7	>4.8
	2 ppm	0.9	2.6	4.5	>4.8
	3 ppm	2.1	4.5	>4.8	>4.8
	4 ppm	3.7	4.8	>4.8	>4.8

TABLE 6
(5 Minutes)

	Log Kill	
Formulation	**Theoretical**	**Actual**
1 ppm Alex/0.3 ppm PHMB	0.8	0.6
2 ppm Alex/0.3 ppm PHMB	0.9	0.8
3 ppm Alex/0.3 ppm PHMB	0.9	1.1
4 ppm Alex/0.3 ppm PHMB	1.2	1.8
1 ppm Alex/0.8 ppm PHMB	0.9	0.9
2 ppm Alex/0.8 ppm PHMB	1.0	0.9
3 ppm Alex/0.8 ppm PHMB	1.1	1.6
4 ppm Alex/0.8 ppm PHMB	1.2	2.8
1 ppm Alex/1.5 ppm PHMB	1.1	1.1
2 ppm Alex/1.5 ppm PHMB	1.2	1.5
3 ppm Alex/1.5 ppm PHMB	1.2	2.6
4 ppm Alex/1.5 ppm PHMB	1.4	3.4

TABLE 7
(15 Minutes)

	Log Kill	
Formulation	**Theoretical**	**Actual**
1 ppm Alex/0.3 ppm PHMB	0.9	1.1
2 ppm Alex/0.3 ppm PHMB	1.1	1.7
3 ppm Alex/0.3 ppm PHMB	1.7	2.7
4 ppm Alex/0.3 ppm PHMB	2.6	3.8
1 ppm Alex/0.8 ppm PHMB	1.5	2.2
2 ppm Alex/0.8 ppm PHMB	1.6	2.8
3 ppm Alex/0.8 ppm PHMB	1.9	3.7
4 ppm Alex/0.8 ppm PHMB	2.6	4.8
1 ppm Alex/1.5 ppm PHMB	1.9	2.9
2 ppm Alex/1.5 ppm PHMB	1.9	3.5
3 ppm Alex/1.5 ppm PHMB	2.1	4.5
4 ppm Alex/1.5 ppm PHMB	2.7	4.8

TABLE 8
(30 Minutes)

	Log Kill	
Formulation	**Theoretical**	**Actual**
1 ppm Alex/0.3 ppm PHMB	1.1	1.8
2 ppm Alex/0.3 ppm PHMB	1.4	2.1
3 ppm Alex/0.3 ppm PHMB	2.0	3.5
4 ppm Alex/0.3 ppm PHMB	3.4	4.8
1 ppm Alex/0.8 ppm PHMB	2.1	3.3
2 ppm Alex/0.8 ppm PHMB	2.2	3.7
3 ppm Alex/0.8 ppm PHMB	2.3	4.8
4 ppm Alex/0.8 ppm PHMB	3.4	4.8
1 ppm Alex/1.5 ppm PHMB	3.1	4.4
2 ppm Alex/1.5 ppm PHMB	3.1	4.5
3 ppm Alex/1.5 ppm PHMB	3.1	4.8
4 ppm Alex/1.5 ppm PHMB	3.6	4.8

TABLE 9
(45 Minutes)

	Log Kill	
Formulation	**Theoretical**	**Actual**
1 ppm Alex/0.3 ppm PHMB	1.2	2.1
2 ppm Alex/0.3 ppm PHMB	1.3	2.6
3 ppm Alex/0.3 ppm PHMB	2.1	4.5
4 ppm Alex/0.3 ppm PHMB	3.7	4.8
1 ppm Alex/0.8 ppm PHMB	3.0	3.7
2 ppm Alex/0.8 ppm PHMB	3.0	4.5
3 ppm Alex/0.8 ppm PHMB	3.1	4.8
4 ppm Alex/0.8 ppm PHMB	38	4.8
1 ppm Alex/1.5 ppm PHMB	4.1	4.8
2 ppm Alex/1.5 ppm PHMB	4.1	4.8
3 ppm Alex/1.5 ppm PHMB	4.1	4.8
4 ppm Alex/1.5 ppm PHMB	4.2	4.8

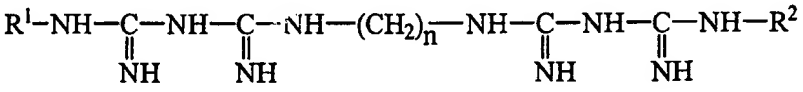
The above results show synergistic microbicidal effects against C. *albicans*, in which the log kill from the combination of both alexidine and PHMB, in a good proportion of cases, is higher than the sum of the individual disinfecting agents, which synergistic effects are evident, beginning with the results after 15 minutes. At 45 minutes, these synergistic effects may become less evident, when a higher proportion of the microorganisms have already been killed. Based on the above data, Figure 1 shows the biocidal efficacy against C. *albicans* of the test solutions containing the combination of alexidine and PHMB, after 15 minutes, compared to the theoretical efficacy, based on the sum of individual solutions containing, respectively, alexidine alone and PHMB alone. Figure 2 shows the biocidal efficacy against C. *albicans* of the test solutions after a period of 30 minutes compared to the theoretical efficacy.

While the invention has been described in conjunction with specific examples thereof, this is illustrative only. Accordingly, many alternatives, modifications, and variations will be apparent to those skilled in the art in light of the foregoing description and it is, therefore, intended to embrace all such alternatives, modifications, and variations as to fall within the spirit and scope of the appended claims.

We claim:

1. A ophthalmically safe disinfecting solution for contact lenses comprising an aqueous solution comprising the following components:

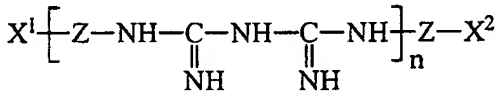
(a) a microbiocidally effective amount of a bis(biguanide) in the amount of about 0.10 to about 4.0 ppm, in the form of a water-soluble salt or the free base, which bis(biguanide) has the following general formula:



(I)

wherein R^1 and R^2 are independently selected from the group consisting of branched or unbranched alkyl having 4-12 carbon atoms, alkoxyalkyl ether or alkylsulfide radical having 4-12 carbon atoms, or cycloalkyl or cycloalkyl-alkyl radical having 5-12 carbon atoms; and n is 4 to 16;

(b) a polymeric biguanide, in the total amount of about 0.10 to about 3.0 ppm, having the formula:



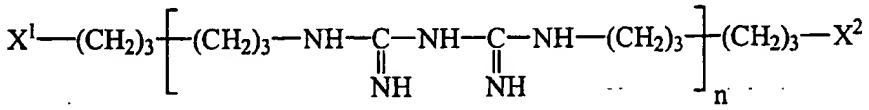
wherein Z is an organic divalent bridging group which may be the same or different throughout the polymer, n is on average at least 3, and X^1 and X^2 are independently selected from the groups $-NH_2$ and -NH - C(=NH) - NH - CN.

(c) an effective amount of a buffering agent; and

(d) water in an amount of at least about 80% by weight.

2. The ophthalmically safe disinfecting solution of claim 1, wherein R^1 and R^2 are independently selected from the group consisting of branched or unbranched alkyl, alkoxyalkyl ether or alkylsulfide thioether radical having 6 to 10 carbon atoms and n is 4 to 10.

3. The ophthalmically safe disinfecting solution of claim 1, comprising a polymeric biguanide that is a mixture of molecules with the general formula:



wherein X^1 and X^2 are as defined above and n is on average 5 to 20.

4. The ophthalmically safe disinfecting solution disinfecting solution of claim 1, further comprising a surfactant in the amount of 0.01 to 5.0 percent.

5. The ophthalmically safe disinfecting solution of claim 4, wherein the surfactant is a neutral or non-ionic surfactant having a plurality of poly(oxyalkylene) chains, each of the poly(oxyalkylene) comprises (-OR) repeat units, wherein R is independently an alkylene having 2 to 6 carbon atoms.

6. The ophthalmically safe disinfecting solution of claim 4, wherein the surfactant is a neutral or non-ionic surfactant which comprises a block copolymer of poly(ethyleneoxide) and poly(propylene oxide) segments.

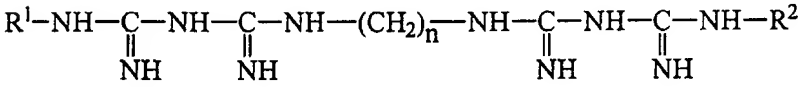
7. The ophthalmically safe disinfecting solution of claim 1, wherein the amount of the bis(biguanide) is 1.0 to 3.0 ppm.

8. The ophthalmically safe disinfecting solution of claim 1, wherein the amount of polymeric biguanide is 0.1 to 2.0 ppm.

9. A method of disinfecting, or cleaning and disinfecting, a soft contact lens with a multipurpose solution or effective multipurpose solution, which method comprises:

(a) soaking the lens in a solution, such that acceptable disinfection of the contact lens is obtained with the solution, the solution comprising, in formulation, the following components:

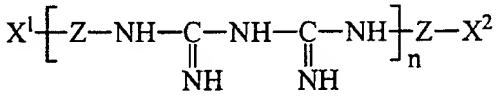
(i) a microbiocidally effective amount of a bis(biguanide) in the amount of about 0.1 to about 4.0 ppm, in the form of a water-soluble salt or the free base, which bis(biguanide) has the following general formula:



(I)

wherein R^1 and R^2 are independently selected from the group consisting of branched or unbranched alkyl having 4-12 carbon atoms, alkoxyalkyl ether or alkylsulfide radical having 4-12 carbon atoms, or cycloalkyl or cycloalkyl-alkyl radical having 5-12 carbon atoms; and n is 4 to 16;

(ii) a polymeric biguanide in the amount of about 0.10 to about 3.0 ppm, which polymeric biguanide has the following general formula:



wherein Z is an organic divalent bridging group which may be the same or different throughout the polymer, n is on average at least 3, and X^1 and X^2 are independently selected from the groups $-NH_2$ and -NH - C(=NH) - NH - CN and;

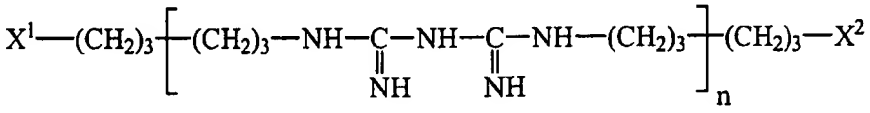
(iii) an effective amount of a buffering agent; and

(b) directly placing the treated lens on the eye of the wearer, wherein (i) rinsing with a different solution prior to replacement on the eye is not required, and (ii) no other solution is required for daily treatment of the lens.

10. The method of claim 9 wherein the method does not include rubbing the lens with the solution, as not required by the instructions for use of the product.

11. The method of claim 9 or 10, wherein R^1 and R^2 are independently selected from the group consisting of branched or unbranched alkyl, alkoxyalkyl ether and alkylsulfide thioether radical, and n is 4 to 10.

12. The method of claim 11, wherein the polymeric biguanide is a mixture of polymeric biguanides having the following formula:



wherein X^1 and X^2 are as defined above and n is on average 5 to 20.

13. The method of claim 9 or 10, wherein the solution is used to clean a lens that is set or planned for replacement after not more than about 30 days of wear.

14. The method of claim 13, wherein the lens is planned or set for replacement after not more than about 14 days of wear.

15. The method of claim 9 or 10, wherein the solution is used to clean a lens that is made from a polymer comprising about 0.0 to 5 mole percent repeat units derived from methacrylic acid (MAA), 10 to 99 mole percent of repeat units derived from hydroxyethyl methacrylate, and about 0.5 to 5 mole percent of cross-linking repeat units and

1/2

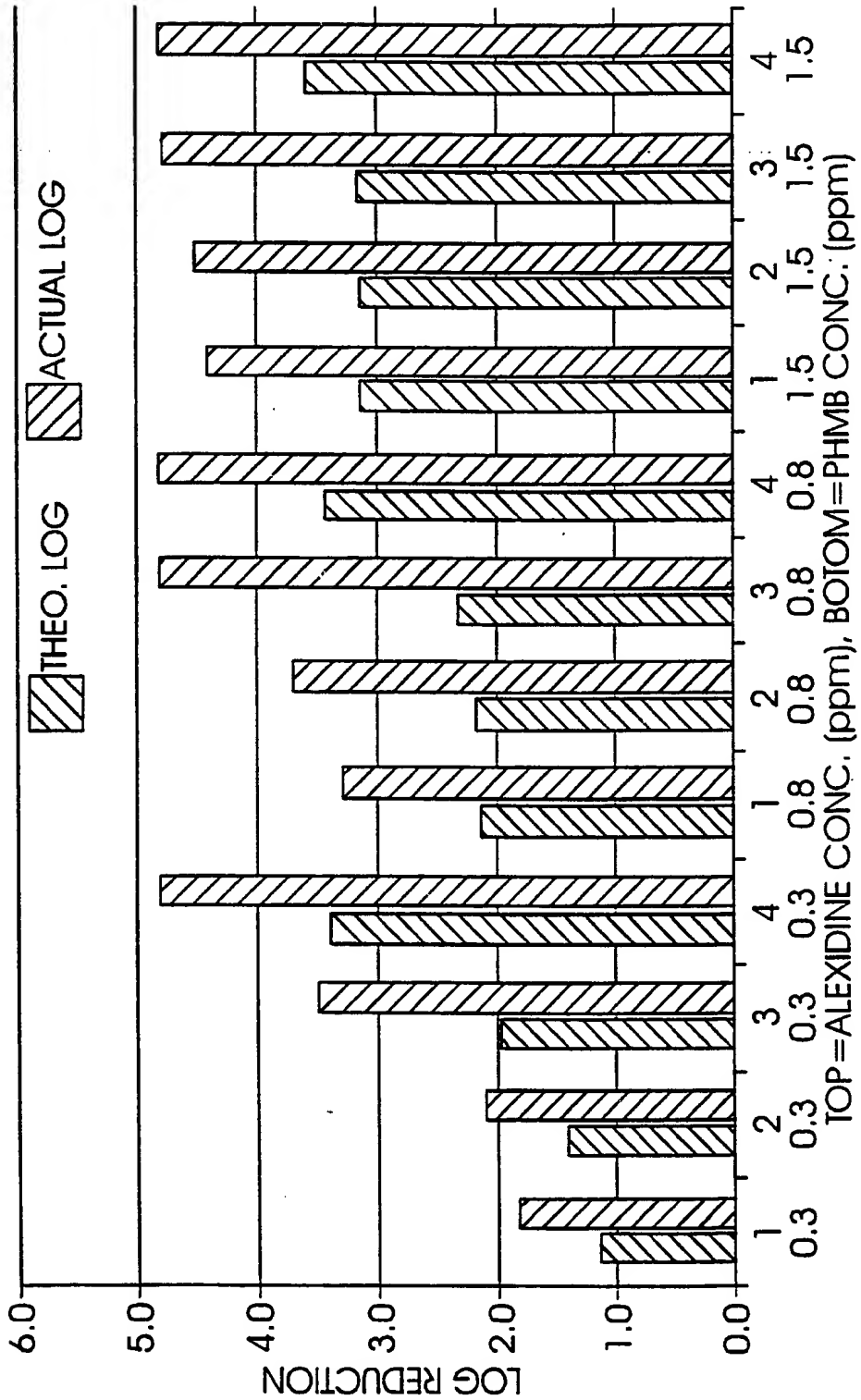

THEO. LOG
ACTUAL LOG
LOG REDUCTION
6.0
5.0
4.0
3.0
2.0
1.0
0.0
TOP=ALEXIDINE CONC. (ppm), BOTOM=PHMB CONC. (ppm)
1 0.3
2 0.3
3 0.3
4 0.3
1 0.8
2 0.8
3 0.8
4 0.8
1 1.5
2 1.5
3 1.5
4 1.5

FIG. 1

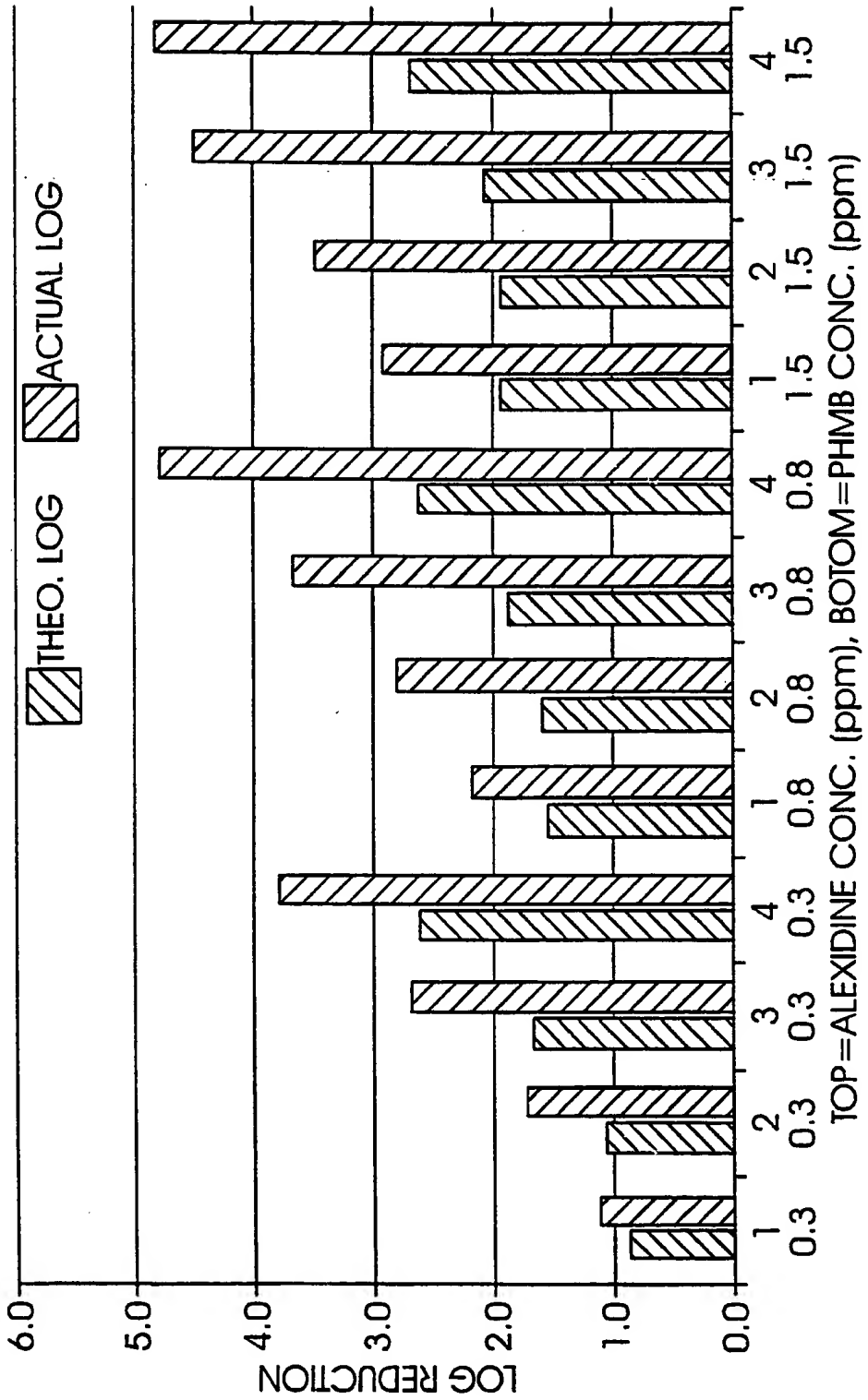

LOG REDUCTION
6.0
5.0
4.0
3.0
2.0
1.0
0.0
THEO. LOG
ACTUAL LOG
TOP=ALEXIDINE CONC. (ppm), BOTOM=PHMB CONC. (ppm)
1 0.3
2 0.3
3 0.3
4 0.3
1 0.8
2 0.8
3 0.8
4 0.8
1 1.5
2 1.5
3 1.5
4 1.5

FIG. 2

INTERNATIONAL SEARCH REPORT

In. ational Application No
PCT/US 98/23818

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C11D3/48 C11D3/32 C11D3/37 A61L2/00 //C11D1/722

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C11D A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 98 20738 A (BAUSCH & LOMB INC.) 22 May 1998 see claims 1-29 ---	1-15
P,X	WO 98 20913 A (BAUSCH & LOMB INC.) 22 May 1998 see page 5, line 25 - page 18, line 25 see claims ---	1-15
A	US 4 758 595 A (OGUNBIYI LAI ET AL.) 19 July 1988 cited in the application see column 3, line 12 - column 9, line 5 see claims --- -/--	1,3-6, 8-10, 12-15

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
9 February 1999	19/02/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Serbetsoglou, A

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INTERNATIONAL SEARCH REPORT

Im ational Application No
PCT/US 98/23818

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 87 00437 A (BAUSCH & LOMB INC.) 29 January 1987 see page 4, line 11 - page 12, line 27 see claims	1,2,4-7, 9-11
A	GB 1 432 345 A (SMITH & NEPHEW RESEARCH LTD.) 14 April 1976 cited in the application see claims; examples 5,6,8	1,3-6, 8-10, 12-15
A	EP 0 701 821 A (TOMEY TECHNOLOGY CORP.) 20 March 1996 see page 2, line 1 - page 5, line 11 see claims	1,3-6, 8-10, 12-15
A	US 5 453 435 A (RAHEJA MANOHAR K. ET AL.) 26 September 1995 cited in the application see claims	1,3,8,9, 12
A	US 4 891 423 A (STOCKEL RICHARD F.) 2 January 1990 see the whole document	1

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ational Application No
PCT/US 98/23818

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